

Applicants have canceled pending claims 51 to 75 without prejudice and substituted therefor claims 76 to 102. This action is intended to advance prosecution of this application and to claim the invention with greater particularity. The claim amendments are discussed more fully below, in response to the Examiner's remarks as a result of examination.

Applicants believe that presentation of the claims in the re-organized contiguous format will facilitate the Examiner's continued review of this application. Applicants' cancellation of claims, which is not to be interpreted as acquiescence to any outstanding rejection, is without prejudice or waiver of their right to pursue the subject matter of those claims in a co-pending application claiming priority herefrom under 35 U.S.C. § 120.

None of the claim amendments constitutes new matter. Support for the substitute claim set is found in the former claims (pending as of the July 21, 2000 Office Action), the originally-filed claims and the specification, as follows:

Substitute Claim No.	Support
76	Original claims 1-7; Former claim 51; Figure 9; Page 32, lines 1-30 of the specification.

77	Original claims 1-7; Former claim 52; Figure 9; Page 32, lines 1-30 of the specification.
78	Original claims 1-7; Former claim 53; Figure 9; Page 32, lines 1-30 and page 29, lines 10-19 of the specification.
79	Original claims 1-7; Former claim 54; Figure 9; Page 32, lines 1-30 of the specification.
80	Former claim 55.
81	Former claim 56.
82	Original claim 16; Former claim 70.
83	Original claim 16; Former claim 71.
84	Original claim 16; Former claim 71. Page 29, lines 10-19 of the specification.
85	Original claim 16; Former claim 70. Page 29, lines 10-19 of the specification.
86	Former claim 59.
87	Former claim 59.
88	Original claim 18; Former claim 59.
89	Former claim 60.
90	Former claim 61.
91	Former claim 62.
92	Former claim 63.
93	Former claim 64.
94	Former claim 65.
95	Original claim 20; Former claim 66.
96	Original claim 20; Former claim 67.

97	Original claim 20; Former claim 67. Page 29, lines 10-19 of the specification.
98	Former claim 68.
99	Former claim 69.
100	Original claim 20; Former claim 72.
101	Original claim 20; Former claim 72.
102	Original claim 20; Former claim 72; Page 29, lines 10-19 of the specification.

The Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner maintained the rejection of claims 51-72, under 35 U.S.C. § 112, first paragraph, on the basis that the the arguments set forth in the prior amendments dated October 28, 1998 and April 26, 2000 were deemed non-persuasive because "they are allegations which are not supported by the level of routine experimentation at the time of filing." More specifically, the Examiner contends that:

-- "in 1983 determination of hybridization conditions that allowed 'specific hybridization' between nucleic acids which differed only by a few nucleotides was not routine."

-- "the specification teaches that under high 'criterium' hybridization conditions the inserts of DR-beta-A,B,C

and D cross hybridize with one another such that the scope of 'specific hybridization' is unclear."

-- "the claims are very broadly drawn to any DNA sequence of any length that can hybridize to some unknown degree of specificity to the specific sequences of the specification."

-- "the claims are drawn to sequences having portions containing any mismatch between these undiscovered hybridizing sequences."

-- "the specification does not teach the locations, identities or sequences of these mismatch regions."

-- "the specification does not provide guidance as to how to make sequences which 'differ' from the specifically disclosed and the large number of 'specifically hybridizing' sequences due to the degeneracy of the genetic code."

-- "the specification does not describe the structure of these oligonucleotides [which contained mismatches] such that the skilled artisan would be able to reasonably predict what they would be without undue experimentation particularly in 1983."

With respect to the new grounds of rejection raised in the July 21, 2000 Office Action, the Examiner states that "claims 51-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention."

The Examiner contends that "the specification has described polynucleotides consisting of DR-beta-A, -B, -C and described the regions within the polypeptide encoded by these polynucleotides, i.e., amino acids 8-14, 24-32 and 72-78, which are variable between -A, -B, and -C and a region which is conserved between -A, -B, and -C, i.e. amino acids 38-45 and describes methods of using these polynucleotides for HLA-DR typing. However, the claims, as written, encompass polynucleotides and methods using polynucleotides that vary substantially in length and nucleotide composition."

With respect to claims 51 and 52, the Examiner contends that "[s]ince the specification has only described three specific DR-beta sequences and because the genus of sequences encompassed by the recitation in the claims is enormous with no common structural features, the three species described in the specification are not representative of the genus." In further purported support of this contention, the Examiner states that "the prior art does not provide compensatory structural or correlative teachings to enable the skilled artisan to identify the DNA sequences encompassed for use in the method."

Applicants believe that the Examiner's contentions are without merit; as addressed more fully below in conjunction with the Declaration of Dr. Richard Lathe, filed concurrently herewith,\* and in response to the previous and newly-raised rejections. As discussed more fully below, applicants have amended the claims to clarify the scope of the intended sequences useful in the HLA-DR typing processes and kits of the present invention.

For example, applicants have amended the claims to recite functionality for DNA sequences useful in the HLA-DR typing processes and kits of this invention -- their ability to hybridize to a specifically defined polymorphic region of an HLA-DR- $\beta$  chain locus of the human lymphocyte antigen complex. In addition, applicants have amended the claims to delete the language of "mismatch" and "portions".

Applicants' invention relates to the discovery that nucleotide sequences encoding the specific polymorphic regions or DNA sequences recited in the claims, or a majority thereof, are useful for HLA-DR typing according to the present invention. One of skill in the art would have appreciated how to use such sequences in order to generate hybridization-based diagnostics.

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\* Applicants' representatives intend to file the executed version of the Lathe Declaration upon receipt from the declarant.

More specifically, by means of sequence analyses of the illustrative HLA-DR- $\beta$ -A and HLA-DR- $\beta$ -B inserts described in the specification, applicants identified amino acid regions 8-14, 26-32 and 72-78 as polymorphic regions among different HLA-DR- $\beta$ -chain genes (page 32, lines 1-30). As illustrated in the application, and acknowledged by the Examiner, HLA-DR typing processes may be carried out using the 19-mers described in the specification. As set forth in the specification, page 31, lines 24-30, at the effective filing date of the present application, hybridization under conditions of Southern blotting with short oligonucleotide DNA fragments had been shown to allow the discrimination of perfect matching sequences (identical or allele) from mismatching sequences (a different sequence or allele). With such knowledge in the art, coupled with applicants' disclosure of the particular DNA inserts and polymorphic regions illustrated herein, one of skill in the art would be able to identify other sequences useful in HLA-DR typing processes and kits according to the present invention.

With such disclosure in hand, combined with applicants' teaching that DR- $\beta$ -A, DR- $\beta$ -B, DR- $\beta$ -C and DR- $\beta$ -D constitute four families of HLA-DR-related sequences, one of skill in the art would clearly recognize how to utilize the nucleotide sequences encoding a majority of the regions defined by amino acids 8-14,

26-32 and 72-78 within the polypeptide encoded by an allelic variant of the HLA-DR- $\beta$ -A and HLA-DR- $\beta$ -B inserts, such as DNA insert HLA-DR- $\beta$ -C (ATCC 39165), in HLA-typing kits and typing processes.

With respect to former claims 53 and 54, the Examiner contends that "Because of the polymorphic nature of these genes, there may be many different DR-beta chain sequences of which three is not representative"; "the claims as written encompass using genomic sequences as well as the cDNA sequences, but the application does not establish that the applicant was in possession of the genomic sequences at the time of the filing"; and "[s]equences identified by hybridization would not predictably have the same structural and functional characteristics as the disclosed species because there is no way to determine what variations would be tolerated without making the method inoperable as a typing method." Applicants disagree.

Applicants refer the Examiner to the Declaration of Richard Lathe, D.Sc., filed concurrently herewith, as expert confirmation that the disclosure of the present application, as filed, and as of its July 30, 1982 effective filing date, enables a person of skill in the art to identify the DNA sequences recited in applicants' claims for use in HLA-DR typing processes and typing kits. For example, as detailed in the Lathe



Declaration, contrary to the Examiner's contention, as of the July 30, 1982, the concept of hybridization was well defined in the art, as "the pairing of two complementary or nearly complementary DNA strands to form a stable duplex". (See, for example, Astell et al., Biochemistry 12, 5068-5074 (1972) [Exhibit F of the Lathe Declaration] and Szostak et al., Methods Enzymol. 68, 419-428 [Exhibit G of the Lathe Declaration]). It was also known that the efficiency of such pairing is a function of both the temperature of the hybridization reaction (which tends to dissociate the duplex) and the salt concentration of the reaction (which tends to associate the duplex). Thus, at any given salt concentration, there is a particular temperature at which the two DNA strands of the hybrid duplex will dissociate from one another. This dissociation was referred to as "melting" and the temperature of melting was designated the "Tm" of the hybrid under the given salt conditions (See Bonner et al., J. Mol. Biol. 81, 123-135 (1973) [Exhibit H of the Lathe Declaration]).

Given the teachings of Bonner, one of skill in the art would have been able to determine the temperature, salt, pH, and buffer regimen to carry out hybridization, as described in the claims of the instant application. For example, as exemplified in applicants' specification [page 31, lines 23-30] hybridization

of short (19 nucleotides) oligonucleotide DNA fragments was achieved under conditions illustrated in Conner et al., Proc. Natl. Acad. Sci. USA 80, 278-282 (1983) [Exhibit I of the Lathe Declaration].

Additionally, as set forth in the Lathe Declaration, and contrary to the Examiner's contention, as of the July 30, 1982, it was known in the art that the specific hybridization conditions used for DNA hybridization are directly related to the probe sequence employed. Specifically, for both long and short hybridization protocols, the thermal stability of the nucleic acid duplex relates closely to the length of the probe used. For long probes, a duplex will remain stable even if a small number of mismatched nucleotides are present. However, short sequences, such as those recited in the claims of the instant application, would be destabilized even by the presence of one or two mismatched nucleotides. (See, for example, Zoller & Smith, Nucleic Acid Res. 10, 6487-6500 [Exhibit K of the Lathe Declaration] and Gillam & Smith, Gene 8, 99-106 [Exhibit L of the Lathe Declaration]).

As also discussed in the Lathe Declaration, as exemplified by Szostak [Exhibit G of the Lathe Declaration], short oligonucleotides, such as those recited in the claims of the instant application, will form stable duplexes only when

there is 100% homology between the probe and the target sequence. Furthermore, Wallace et al. Nucleic Acid Res. 9, 3647-3656 (1981) [Exhibit M of the Lathe Declaration] teaches the hybridization conditions under which a 19-mer oligonucleotide probe containing a single nucleotide change will only form a duplex with the 100% sequence identical complementary DNA molecule and not with a complementary nucleotide sequence which has a single base pair mismatch. Finally, as cited in applicants' specification, Conner [Exhibit I of the Lathe Declaration] teaches, in detail, the conditions that permit the detection of single or multiple mismatches using a 19-mer probe. Accordingly, with applicants' disclosure in hand, and in view of knowledge in the art as of the effective filing date of this application, it is clear that a person of skill in the art would be able to determine those DNA sequences useful in the HLA-DR typing processes and kits encompassed by the claims of the present application. Once applicants identified amino acid regions 8-14, 26-32 and 72-78 as polymorphic regions of an HLA-DR- $\beta$  chain locus of the human lymphocyte antigen complex, they also made possible DNA sequences which hybridize to said regions. Such hybridizing sequences would, in turn, be appreciated by those of skill in the art as being useful for HLA-DR typing. As set forth in the Lathe

Declaration, determination of such hybridizing sequences was well within the skill of the art as of July 30, 1982.

Finally, the Examiner contends that "the claims as written encompass using genomic sequences as well as the cDNA sequences but the genomic DNA sequence has not been described in the specification to establish that applicant was in possession of genomic sequences at the time of filing." Applicants disagree, based on the claims amendments herein.

Applicants have amended the claims to recite functionality for DNA sequences useful in the HLA-DR typing processes and kits of this invention -- their ability to hybridize to a specifically defined polymorphic region of an HLA-DR- $\beta$  chain locus of the human lymphocyte antigen complex. Such sequences do not include genomic DNA.

The Examiner has cited no evidence in support of her opinion of non-enablement. In the absence of evidence to the contrary, the Examiner has no reason to doubt the objective truth of applicants' asserted operability of the present invention:

"As a matter of Patent Office practice ... a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented, must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied

upon for enabling support... [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." Ex parte Kenaga, 189 USPQ 62, 64 (Pat. Off. Bd. Pat. App. 1975), quoting In re Marzocchi, 439 F.2d 220, 223-24, 169 USPQ 367, 369 (CCPA 1971) (emphasis in original).

For all of the foregoing reasons, the Examiner should withdraw the § 112, first paragraph rejection.

The Examiner also maintains that claims 57-65 and 70-71 "are not supported by the description in the specification because the claims encompass typing method[s] using a DNA sequence which minimally, encoded 'a majority' of a region of amino acids 8-14, 26-32, or 72-78 of HLA-DR-beta -A, -B, -C or allelic variants" and "[t]he claims are broadly drawn to a huge number of different typing methods using completely different probes when only three specific DR-beta chain sequences have been described." Applicants traverse.

Applicants believe that their disclosure clearly supports more than three specific DR-beta chain sequences, including both fragments and portions of applicants' DNA inserts (i.e., HLA-DR- $\beta$ -A, HLA-DR- $\beta$ -B and HLA-DR- $\beta$ -C:

More particularly, as set forth in the specification:  
"The cDNA inserts coding for families of HLA-DR- $\beta$ -chain

antigens or fragments thereof may be used in DR typing processes and kits. In general such typing processes comprise the steps of ... (3) hybridizing the size fractionated DNA to the HLA/DR- $\beta$ -chain related probes of this invention or fragments thereof and ...." (specification, page 29, lines 10-19, emphasis added).

In view of applicants' disclosure, one of skill in the art could readily prepare fragments of the illustrative DNA inserts useful for HLA-DR- $\beta$  typing processes and kits.

Additionally, at applicants' effective filing date, allelic variants were recognized in the art as alternate forms of a given DNA sequence which may have a substitution, deletion, or addition of one or more nucleotides. (See, for example, Zoller & Smith, [Exhibit L of the Lathe Declaration] and Gillam & Smith, [Exhibit M of the Lathe Declaration]). Such sequences are disclosed in the specification at page 35, lines 12-33.

Furthermore, given the disclosure of applicants' three specific DR-beta chain sequences (i.e., HLA-DR- $\beta$ -A, HLA-DR- $\beta$ -B and HLA-DR- $\beta$ -C) it would be possible for a person of skill in the art to determine the specific hybridization conditions necessary to determine additional DNA sequences capable of hybridizing to a polymorphic region of the HLA-DR- $\beta$  chain locus of the human lymphocyte antigen complex according to the present application, without undue experimentation, based on the skill of the art, and modified accordingly by the incorporation of the proper control DNA sequences.

Finally, applicants note that the Examiner has cited no evidence in support of her opinion, see supra.

The Examiner further contends that, with respect to claims 51, 53, 55, 57, 59, 60, 62, 64 and 70, "the specification, while being enabling for an HLA-DR typing method comprising restricting DNA, size fractionating the restricted DNA and then hybridizing the specifically recited sequences, does not reasonably provide enablement for an HLA-DR typing method comprising hybridizing DNA in a sample with the specifically recited sequences." The Examiner further contends that "[s]ince all individuals have a DR beta chain locus and since the specification teaches that sequences from the different loci cross hybridize, a hybridization assay which did not generate a fractionated restriction pattern would not distinguish individuals since the DR-beta -A, -B, and -C sequences would be expected to cross hybridize to most samples. That is, the detection of hybridization does not appear to be useful for typing, but instead the pattern of hybridization using the different disclosed probes." Applicants disagree.

The claims which recite the steps of hybridization and detection, rather than generation of a fractionated DNA restriction pattern, would be useful as HLA-DR typing processes. For example, such steps constitute a base-line screening assay

(i.e., a first level typing), whereby detection of the presence or absence of an HLA-DR- $\beta$  chain in a sample indicates the relative level of risk that a person has for becoming susceptible to a given disease. Such a process would serve as a first level assessment, which could be followed up by further diagnostic steps, in order to provide direct disease diagnosis for a given individual or to specify a particular HLA-DR- $\beta$  type of a given sample. Accordingly, those of skill in the art would recognize the utility of the disclosed probes in conjunction with the detection of hybridization, for HLA-DR typing, even in the absence of the generation of a fractionated restriction pattern.

The Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 51 to 75 stand rejected, under 35 U.S.C. § 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." More particularly, the Examiner contends that claims 51, 52, 60-66 and 68 are "indefinite" in reciting "the expressed portion of the DNA sequence of DNA insert DR-beta-A, DR-beta-B or DR-beta-C" because this phrase make the claims unclear as to the metes and bound of "the DNA sequence". Applicants have obviated this contention by amending the claims to delete the objected-to phrase.



Additionally, the Examiner contends that claims 57, 59, 60, 62 and 75 are "indefinite" in reciting "encoding a majority of the region . . .", because as written the claims are unclear as to what would be encompassed by "a majority". Applicants state that one of skill in the art, at the filing date of the application, would understand that the phrase "encoding a majority of the region . . ." to encompass "more than 51% of the encoding region".

Finally, the Examiner contends that claim 59 is "indefinite" in reciting "said second DNA" because this term lacks antecedent basis in claim 57. Applicants have obviated this rejection by cancellation of claims 57 and 59.

#### The Rejections Under 35 U.S.C. § 102(b)

The Examiner has rejected the claims under 35 U.S.C. § 102(b) as being "anticipated" by Larhammar et al., Proc. Natl. Acad. Sci. USA 79, 3687-3691 (1982) which the Examiner believes "teach[es] an isolated DNA sequence which encodes the complete amino acid sequence of the HLA-DR antigen beta chain (see Figure 2)." Applicants believe that the DC- $\beta$  chain sequence described by Larhammar does not anticipate or render obvious the use of the HLA-DR- $\beta$ -A, HLA-DR- $\beta$ -B and HLA-DR- $\beta$ -C sequences and the regions

of mismatch between these two sequences, in HLA-DR typing processes and kits according to the present application.

The Examiner's contention appears to stem from a basic misinterpretation of nomenclature employed by Larhammar and by applicants herein. Larhammar purports to disclose the nucleotide sequence of an "HLA-DR antigen-like  $\beta$ -chain cDNA clone" and to demonstrate that his predicted amino acid sequence is homologous to the corresponding regions of HLA-A, HLA-B and HLA-C antigen heavy chains. As detailed below, although Larhammar characterizes his cDNA clone as an "HLA-DR antigen-like  $\beta$ -chain", the DNA sequence of his clone is that of a DC- $\beta$ -chain. The DNA sequences and inserts useful in the HLA-DR typing processes and kits of the present invention, however, correspond to HLA-DR- $\beta$ -chain antigens, not the HLA-A, -B or -C antigens to which Larhammar's cloned cDNA is purportedly homologous. As such, the DNA sequence of Larhammar's clone does not teach or suggest applicants' HLA-DR- $\beta$ -A or HLA-DR- $\beta$ -B DNA inserts, or any portions thereof.

More particularly, as depicted in Figure 6 of the present application, the amino acid sequence deduced from Larhammar's pDR- $\beta$ -1 cDNA insert differs from that of applicants' HLA-DR- $\beta$ -A DNA insert. As also demonstrated in Figure 6, where the boxed portion indicates the trans-membrane region of each

sequence, the cytoplasmic portion of applicants' DR- $\beta$ -chain differs in both composition and length (16 amino acids vs. 8 amino acids) from that of Larhammar's cDNA clone.

Furthermore, as stated in the instant specification at page 28, line 25 to page 29, line 2, the amino acid sequence of Larhammar's cDNA clone is believed to be a DC- $\beta$ -chain, not a DR- $\beta$ -chain, because it matches the partial N-terminal sequence determined for the DS- $\beta$ -chain (see S.M. Goyert et al., J. Exp. Med., 156, pp. 550-66 at p. 561 (1982), copy enclosed). DS and DC antigens are identical and show a high degree of homology with the mouse I-A Ia antigens (see M.R. Bono and J.L. Strominger, Nature, 299, pp. 836-38 (1982), copy enclosed). In contrast, DR antigens are homologous with the mouse I-E/C antigen, as assessed by N-terminal amino acid sequencing, serological cross-reactions and other structural and functional similarities (see D.A. Shackelford, Immunol. Rev., 66, pp. 133-87 at p. 174 (1982), copy enclosed).

The distinction from Larhammar is further supported by D. Owerbach et al., Proc. Natl. Acad. Sci., USA, 80, pp. 3758-61 (1983), copy enclosed. Owerbach employed Larhammar's pDR- $\beta$ -1 cDNA to probe restriction enzyme-digested DNA from HLA-D homozygous typing cells. In characterizing Larhammar's cDNA clone, Owerbach stated that:

"the present  $\beta$ -chain cDNA probe was isolated from a cDNA clone separate from the HLA-DR  $\beta$ -chain locus...it does not correspond to the I-E/C region, the murine counterpart to human HLA-DR, but rather to the human equivalent of the murine I-A  $\beta$ -chain locus." (page 3760)

In K. Gustafsson et al. EMBO J., 3, pp. 1655-61 (1984), copy enclosed, Larhammar, a co-author of the article, acknowledges that the pDR- $\beta$ -1 clone referred to in his earlier article is in fact a DC- $\beta$ -cDNA clone, which is renamed as pII- $\beta$ -1 "to avoid confusion with the DR pDR $\beta$  clones" (page 1656). Additionally, J. Bohme et al., Nature, 301, pp. 82-84 (1983), copy enclosed, refers to Larhammar's cDNA clone as:

"a cDNA clone distinct from the DR  $\beta$ -chain locus. This cDNA clone probably corresponds to the human equivalent of the murine I-A  $\beta$ -chain locus." (page 82).

The identification of Larhammar's cDNA clone as a DC- $\beta$ -cDNA clone is further supported in Table I of Gustafsson (page 1657), which demonstrates that pII- $\beta$ -1 shares 92% homology with DC- $\beta$ -chain clones. After identifying the Larhammar clone as a DC- $\beta$ -chain clone, Gustafsson points out distinctions between DC- $\beta$ -chain and DR- $\beta$ -chain antigens:

"The differences between the conserved parts of the DR $\beta$  and DC $\beta$  chains may also suggest that the two types of class II antigens fulfill somewhat different physiological functions." (page 1658)

"The class II antigens differ from the polymorphic class I antigens in that sequences from different class II loci form well-defined groups with respect to

homology.... Therefore, it is unlikely that genetic information is frequently exchanged between different class II loci." (page 1660)

It is clear from the foregoing that Larhammar discloses a DC  $\beta$ -chain clone, which neither teaches nor suggests applicants' DR  $\beta$ -chain sequences, which are useful in HLA-DR typing processes and kits. Furthermore, even if Larhammar disclosed DR  $\beta$ -chain sequences, which it does not, the article does not teach or suggest HLA-DR typing processes or kits using (1) DNA sequences which hybridize to a polymorphic region of an HLA-DR- $\beta$ -chain locus of the human lymphocyte antigen complex or (2) the specific DNA inserts recited in the claims. Accordingly, Larhammar does not anticipate or render obvious any claim of this application.

#### Obviousness-type Double Patenting Rejection

The Examiner also maintained the rejection of claims 51 to 75 under the judicially created doctrine of obviousness-type double patenting as being "unpatentable" over claims 1 to 10 of United States Patent No. 5,503,976. Upon indication of allowable claims in this application, applicants stand ready to file a Terminal Disclaimer, should the Examiner assert the double patenting rejection against added claims 76 to 102.

Applicants request that the Examiner consider the

foregoing amendments and remarks and pass this application to  
issue.

Respectfully submitted,

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